Institution: Imperial College London

Unit of Assessment: 04 Psychology, Psychiatry and Neuroscience

Title of case study: FLAIR MRI: Transforming Brain Imaging for Neurological Disease

1. Summary of the impact (indicative maximum 100 words)

The FLAIR (Fluid Attenuated Inversion Recovery) MRI sequence developed at Imperial College has transformed the sensitivity of clinical neuroimaging for white matter brain lesions. FLAIR has had significant commercial impact with incorporation as a standard imaging sequence offered by *all* manufacturers on their MRI scanners. The inclusion of FLAIR in routine diagnostic MRI protocols in radiology centres worldwide provides evidence of the continued extensive reach of impact for better healthcare outcomes through improved diagnosis and management. The use of FLAIR has led to more powerful Phase II trial designs for development of medicine for stroke, neuroinflammatory disorders, epilepsy and neuro-oncology based on imaging outcomes.

2. Underpinning research (indicative maximum 500 words)

Key Imperial College London Researchers:
Professor Graeme Bydder, Professor of Radiology (1981-1997), Honorary Professor (2000-2006)
Professor Jo Hajnal, Professor of Imaging Science (2002-2012)
Professor Ian Young, Visiting Professor, (1983- 2004), Senior Research Investigator (2004-present)

Magnetic Resonance Imaging (MRI) scanners use radio waves applied in a strong magnetic field to detect signals from protons, which are predominantly in water molecules in body tissues. These signals can then be used to re-construct an anatomical image. By varying scanner pulse sequence parameters ("weighting" some of them selectively), different tissues or pathological processes can be emphasised.

The combination of engineering, physics and clinical imaging expertise in the Robert Steiner Unit at Imperial College's Hammersmith Hospital campus provided a unique environment for world leading development and rapid translation of novel MRI technologies from its first introduction as an experimental imaging method. Professors Bydder, Hajnal, and Young, led pioneering research in development of the methods, establishing the neuropathological correlates of MRI signal changes and in defining the interaction between MRI parameters and tissue contrast in radiological applications. This work has led to improvements in MRI hardware, new pulse sequences and sources of image contrast, and optimisation of MRI for detection of pathology particularly for neurological diseases. It was in the context of this broad range of underpinning research that the Fluid Attenuated Inversion Recovery (FLAIR) MRI sequence was developed, refined and first applied to address major clinical diagnostic problems.

The FLAIR sequence was highly innovative at the time of its development because it applied conventional "T2-weighting" (images particularly sensitive to tissue fluid, which appear bright) whilst selectively nulling the large signal contribution from water in the cerebrospinal fluid (CSF) and perivascular spaces around the brain (1). The FLAIR sequence thus highlights pathological accumulations of water in the brain, e.g., in tissue damaged by a stroke or from the oedema associated with inflammation or neoplasms.

Studies from Professor Bydder and his colleagues established that this selective contrast delivers increased sensitivity and specificity for detection of brain pathologies when compared with conventional T2- or proton density weighted sequences (2). By affording greater contrast between healthy and pathological tissues, FLAIR allows earlier detection and more reliable anatomical delineation to diagnosis and management of focal brain or brainstem lesions as diverse as infarctions, demyelinating disease, sarcoidosis or metastatic tumours (2). The method has particular value for detecting cortical brain lesions or lesions of the spinal cord (3) for which the

benefits of being able to differentiate neural tissue from the large amount of adjacent CSF is particularly important and for enabling the detection of blood in the CSF.

However, the original FLAIR sequence was prone to artifacts related to flow and pulsation in the CSF and around blood vessels, which limited clinical usefulness, especially in applications to the spinal cord. Since 2001, developments and refinement of the FLAIR sequence by the Hammersmith team have minimised these artefacts substantially and thus further improved the sensitivity of the method (4, 5, 6). With these further refinements, FLAIR has revolutionised neurological imaging. The sequence is a "gold standard" diagnostic sequence for many applications that is used in clinical practices worldwide.

3. References to the research (indicative maximum of six references)

(1) Oatridge, A., Hajnal, J.V., Cowan, F.M., Baudouin, C.J., Young, I.R., Bydder, G.M. (1993). MRI diffusion-weighted imaging of the brain: contributions to image contrast from CSF signal reduction, use of a long echo time and diffusion effects. *Clin Radiol,* 47(2), 82-90. DOI. Times cited: 12 (as at 8th November 2013 on ISI Web of Science). Journal Impact Factor: 1.81

(2) Thomas, D.J., Pennock, J.M., Bydder, G.M., Steiner, R.E., J.V. Hajnal, Young, I.R. (1993). Magnetic resonance imaging of spinal cord in multiple sclerosis by fluid-attenuated inversion recovery. *Lancet,* 341 (8845), 593–594. DOI. Times cited: 63 (as at 8th November 2013 on ISI Web of Science). Journal Impact Factor: 39.06

(3) De Coene, B., Hajnal, J.V., Pennock, J.M., Bydder, G.M. (1993). MRI of the brain stem using fluid attenuated inversion recovery pulse sequences. *Neuroradiology,* 35(5), 327-331. Times cited: 69 (as at 8th November 2013 on ISI Web of Science). Journal Impact Factor: 2.7

(4) Curati, W.L., Oatridge, A., Herlihy, A.H., Hajnal, J.V., Puri, B.K., Bydder, G.M. (2001). Contributions of an adiabatic initial inversion pulse and K-space re-ordered by inversion-time at each slice position (KRISP) to control of CSF artifacts and visualization of the brain in FLAIR magnetic resonance imaging. *Clin Radiol*, 56(5), 375-384. DOI. Times cited: 0 (as at 8th November 2013 on ISI Web of Science). Journal Impact Factor: 1.81

(5) Herlihy, A.H., Oatridge, A., Curati, W.L., Puri, B.K., Bydder, G.M., Hajnal, J.V. (2001). FLAIR imaging using nonselective inversion pulses combined with slice excitation order cycling and k-space reordering to reduce flow artifacts. *Magn Reson Med*, 46 (2), 354-64. DOI. Times cited: 8 (as at 8th November 2013 on ISI Web of Science). Journal Impact Factor: 3.26

(6) Herlihy, A.H., Hajnal, J.V., Curati, W.L., Virji, N., Oatridge, A., Puri, B.K., Bydder, G.M. (2001). Reduction of CSF and blood flow artifacts on FLAIR images of the brain with k-space reordered by inversion time at each slice position (KRISP). *AJNR Am J Neuroradiol,* 22 (5), 896-904. Times cited: 15 (as at 8th November 2013 on ISI Web of Science). Journal Impact Factor: 3.16

4. Details of the impact (indicative maximum 750 words)

Impacts include: health and welfare, commerce, practitioners and services
Main beneficiaries include: patients, health services providers, industry

Development of the FLAIR sequence and its subsequent refinement have improved the sensitivity of MRI as a diagnostic technique by minimising confounds from normal brain water to selectively enable sensitive detection of pathological fluid accumulations in tissue or blood in CSF (1). This has allowed FLAIR to have a substantial clinical impact by improving diagnosis and patient management in neuroradiological practices worldwide. FLAIR is used as a key diagnostic sequence in almost all clinical brain MRI protocols for diagnosis and monitoring of a broad range of neurological disorders. Impact has been particularly significant for imaging in Multiple Sclerosis (MS) and related inflammatory disorders, stroke and epilepsy. FLAIR is recommended in imaging guidelines and is part of diagnostic criteria use internationally for MRI assisted diagnosis and

therapeutic response evaluations [1, 2]. FLAIR is also increasingly utilised for neuro-oncology imaging in both clinical management and drug trials [3].

Commercial impact also has been significant. FLAIR (or a variant based on FLAIR in the case of Siemens scanners) is included as a standard brain imaging sequence by all manufacturers of clinical MRI scanners. The global market for MRI systems was estimated to be £4.3 billion in 2010, and is expected to grow to around £6.2 billion by 2015, equivalent to an annual growth of 7.7% a year [4]. MRI systems made a direct value-added contribution to UK GDP of around £54 million (in 2010 prices) [5], FLAIR is incorporated into all of the new MRI machines sold globally [6].

Currently the greatest demand for MRI procedures in the US is for brain MRI, with spinal MRI scans running a close second. FLAIR is used routinely in almost all neurological scanning and particularly for brain scanning, which constitutes a substantial proportion: 25-30% of all MRI examinations include brain imaging [7]. It has been estimated that there are over 20 million FLAIR examinations per annum worldwide [7].

Further indirect commercial impact has resulted through incorporating FLAIR measures as endpoints in commercial clinical trials (for example in evaluation of treatment responses for MS, stroke and cancers [8]). By enhancing sensitivity to disease changes, FLAIR imaging has increased the effect size in early phase trials, hence reducing numbers in trials, timescale and cost [8].

With increasing clinical demand for MRI as a pivotal tool in clinical decision making, FLAIR has contributed to more time-efficient (and hence cost-efficient) clinical diagnostic protocols, while also improving potential diagnostic sensitivity [9]. FLAIR is the T2-weighted imaging sequence of choice. It has notably contributed to improving risk stratification for patients presenting after a first demyelinating episode (clinically isolated syndrome), allowing early treatment and thus delaying the onset of clinically definite MS [10].

5. Sources to corroborate the impact (indicative maximum of 10 references)

As is common practice, acronyms for techniques commonly used in imaging become incorporated into technical language; FLAIR is so ubiquitous in clinical brain MRI, that the original research and development of the techniques are now rarely referenced directly.

[1] American College of Radiology: Practice Guidelines (2013)
- ACR–ASNR Practice Guideline for the Performance of MRI of the Adult Spine http://www.acr.org/~/media/ACR/Documents/PGTS/guidelines/MRI_Adult_Spine.pdf (archived on 8th November 2013)
- ACR–ASNR–SPR Practice Guideline for the Performance and Interpretation of MRI of the Brain http://www.acr.org/~/media/ACR/Documents/PGTS/guidelines/MRI_Brain.pdf (archived on 8th November 2013)

[2] Acute Stroke Imaging: FLAIR inclusion in MR "Fast" protocol http://www.gehealthcare.com/euru/cardiology/clinical-case/acute-stroke-imaging.html (archived on 8th November 2013)

[3] Pope, W.B., Hessel, C. (2011). Response Assessment in Neuro-Oncology Criteria: Implementation Challenges in Multicenter Neuro-Oncology Trials. *Am J Neuroradiol*, 32, 794-797. DOI

[4] Global MRI Market Size (2010). http://bccresearch.blogspot.co.uk/2010/09/global-market-for-mri-systems-to-grow.html Archived on 8th November 2013

[5] Economic Impact of MRI: Oxford Economics: Economic impact of physics research in the UK: MRI scanners case study November 2012. Archived on 8th November 2013.

[6] Commercial Impact: FLAIR sequence incorporated into all MRI machines – see MRI operating protocols for the following market leaders:

- Siemens: http://www.healthcare.siemens.co.uk/magnetic-resonance-imaging (archived 8th November 2013)
- Philips Medical: http://www.healthcare.philips.com/us_en/products/mri/ (archived on 8th November 2013)
- GE Healthcare: http://www3.gehealthcare.co.uk/en-GB/Products/Categories/Magnetic_Resonance_Imaging (archived on 8th November 2013)

FLAIR sequences in standard commercial protocols from all major manufacturers. For example, Siemens (http://www.gobookee.net/search.php?q=mri+siemens+brain+protocols – archived on 8th November 2013)

[7] Use of FLAIR in neurological scanning and mumber of MRI scans per year and breakdown of area scanned:

- Letter from the President of the British Society of Neuroradiologists
- http://www.magnetica.com/page/innovation/todays-mri-market/

[8] End Points in Clinical Trials
Multiple sclerosis:

- Efficacy of treatment of MS with IFNbeta-1b or glatiramer acetate by monthly brain MRI in the BECOME study. 2009

Neuro-oncology:

- Updated response assessment criteria for high-grade gliomas: response assessment in neuro-oncology working group. 2010
- Response assessment in neuro-oncology (a report of the RANO group): assessment of outcome in trials of diffuse low-grade gliomas. 2011

Epilepsy:

- Core elements of epilepsy diagnosis and management: expert consensus from the Leadership in Epilepsy, Advocacy, and Development (LEAD) faculty. 2008

[9] Cost-efficient investigation:
Two-tiered approach to MRI for headache: a cost-effective way to use an expensive technology. 2013.

[10] Improved outcome with early diagnosis in multiple sclerosis
Diagnostic criteria for multiple sclerosis: 2010 revisions to the McDonald criteria. DOI